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The role of macrophages in obesity-associated islet inflammation and β -cell abnormalities

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Abstract | Chronic, unresolved tissue inflammation is a well-described feature of obesity, type 2 diabetes mellitus (T2DM) and other insulin-resistant states. In this context, adipose tissue and liver inflammation have been particularly well studied; however, abundant evidence demonstrates that inflammatory processes are also activated in pancreatic islets from obese animals and humans with obesity and/or T2DM. In this Review, we focus on the characteristics of immune cell-mediated inflammation in islets and the consequences of this with respect to β -cell function. In contrast to type 1 diabetes mellitus, the dominant immune cell type causing inflammation in obese and T2DM islets is the macrophage. The increased macrophage accumulation in T2DM islets primarily arises through local proliferation of resident macrophages, which then provide signals (such as platelet-derived growth factor) that drive β -cell hyperplasia (a classic feature of obesity). In addition, islet macrophages also impair the insulin secretory capacity of β -cells. Through these mechanisms, islet-resident macrophages underlie the inflammatory response in obesity and mechanistically participate in the β -cell hyperplasia and dysfunction that characterizes this insulin-resistant state. These findings point to the possibility of therapeutics that target islet inflammation to elicit beneficial effects on β -cell function and glycaemia.

The global prevalence of type 2 diabetes mellitus (T2DM) continues to increase at a considerable rate, with a corresponding rise in morbidity and mortality, which places a growing burden on health-care systems¹. Insulin resistance is a key antecedent pathophysiological feature in T2DM. The great majority of patients with T2DM are also obese, and obesity is far and away the major cause of insulin resistance in humans. Thus, obesity and T2DM are closely linked, and the parallel worldwide increases in obesity rates are the main driver of the T2DM epidemic. Many of these individuals with obesity are prediabetic, in that they will eventually develop T2DM. The rates of conversion can be 2–10% per year, depending on the population under study and the means of assessment^{2,3}. However, not all individuals with obesity develop T2DM. In those patients who do progress, a second metabolic defect occurs in addition to insulin resistance, involving β -cell dysfunction^{4,5}. In T2DM, β -cells can no longer secrete excessive amounts of insulin to compensate for the insulin resistance, and hyperglycaemia ensues. There is an enormous literature available on β -cell dysfunction in T2DM. For example, glucotoxicity, lipotoxicity, genetic defects, oxidative

responses, endoplasmic reticulum (ER) stress, inflammation and other mechanisms have all been implicated as causally related to decreased insulin secretion from β -cells⁶.

Obesity is well known to confer a state of chronic low-grade inflammation, particularly in adipose tissue and liver^{7–9}. Many studies point to this inflammatory state as an underlying mechanism for the development of insulin resistance in obesity and T2DM. A number of papers have now demonstrated that this chronic tissue inflammatory state also occurs in pancreatic islets^{10–12}. Islet inflammation has been described in a variety of mouse models of obesity and T2DM as well as in human islets from patients with obesity and/or T2DM¹⁰. The mechanisms leading to islet inflammation are incompletely understood, but it is likely that islet inflammation contributes to the β -cell dysfunction that characterizes T2DM.

In this Review, we focus on the concept of islet inflammation, with particular attention paid to the innate immune system (that is, macrophages). We discuss the distribution and accumulation of macrophages in pancreatic islets in normal and obese conditions and how macrophages influence β -cell abnormalities (BOX 1).

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Key points

- Macrophages are the primary immune cells involved in obesity-associated islet inflammation in both mice and humans.
- Obesity reprogrammes the islet immune microenvironment by inducing the local replication of islet-resident macrophages or by recruiting circulating monocytes.
- Islet macrophages in obese mice display multiple functions, including decreasing β -cell insulin secretion and stimulating β -cell proliferation.
- In the normal, lean state, islet macrophages promote islet development and maintenance of normal glucose-stimulated insulin secretion.
- Islet macrophages are potential therapeutic targets to modulate β -cell function in individuals with obesity and/or type 2 diabetes mellitus.

Macrophages in pancreatic islets

During embryonic development and at steady state.

Tissue macrophages can be acquired during development or can differentiate from circulating monocytes¹³. Studies in mice show that, during embryonic development, macrophages in the pancreas are derived from yolk sac-derived primitive haematopoiesis¹⁴. These pancreatic macrophages are found in close proximity to insulin-positive β -cells¹⁴, and additional studies suggested that these macrophages are involved in islet morphogenesis¹⁵. Consistent with this idea, a mouse model of osteopetrosis (*op/op* mice), which lacks colony-stimulating factor 1 (CSF1) and has a deficit in macrophage development, showed decreased pancreatic islet development and β -cell expansion^{15,16}.

Pancreatic macrophages display heterogeneous phenotypes depending on developmental stage^{15,17}, anatomical location^{12,17} or the metabolic setting¹². With respect to the latter, using immunostaining of macrophage-specific plasma membrane proteins (for example, the adhesion F4/80 and the integrin CD11c) and flow cytometry analyses, researchers found that pancreatic islets harboured two phenotypically distinct macrophage subsets at steady state. A F4/80^{lo}CD11c⁺ population was enriched within the islets (intra-islet macrophages), whereas F4/80^{hi}CD11c⁻ macrophages largely resided in the peripheral islet area (known as peri-islet macrophages)¹². Knowledge about the role of these pancreas-resident or islet-resident macrophages at steady state remains incomplete. In addition to promoting islet organogenesis^{16,17}, how pancreatic macrophages participate in tissue homeostasis and the function of β -cells remains to be fully defined.

Inflammation in T2DM islets. Tissue inflammation is characterized by the accumulation and differentiation of various types of immune cell in local pathological lesions^{18–21}. Macrophages are key cell types that orchestrate the initiation, specification and resolution of tissue-specific inflammation^{9,22,23} (BOX 2). Numerous studies have revealed that macrophage infiltration is increased in T2DM islets and that the number of islet-resident macrophages generally correlates with the degree of β -cell dysfunction^{24–29}. Of note, insulinitis is well known as a feature common to both type 1 diabetes mellitus (T1DM) and T2DM islets derived from humans; however, a clear distinction exists between these two conditions — in T2DM islet inflammation, macrophages dominate, whereas both innate and adaptive

immune cells are heavily involved in T1DM islets¹¹. For example, the number of CD68⁺ (a macrophage-specific plasma membrane protein) macrophages is reportedly increased in human and mouse T2DM islets without changes in the number of CD3⁺ T cells²⁴. Moreover, the same study found that the majority of CD68⁺ macrophages were positive for tissue-resident macrophage markers, such as CD163 and HLA2. In another study, the number of CD68 and inducible nitric oxide synthase double-positive macrophages increased in islet amyloid polypeptide (IAPP)-positive T2DM islets, without changes in numbers of CD163⁺ and CD204⁺ M2-like macrophages²⁵, suggesting that T2DM is associated with increased pro-inflammatory M1-like macrophage accumulation in pancreatic islets.

Obesity-associated islet inflammation. Islet inflammation has been reported in individuals with obesity, characterized by the accumulation of immune cells^{10–12,29} along with elevated production of inflammatory cytokines and chemokines^{29–31}. Furthermore, studies have reported increased numbers of myeloid-lineage cells (primarily monocytes and macrophages) in the islets of obese animal models^{10,24,27,32}. The first comprehensive analysis of obesity-associated islet macrophages used CD68 and CD11b as markers and found an increased number of macrophages in the pancreas of high-fat diet (HFD)-fed C57BL/6J mice and Goto-Kakizaki rats²⁴. Moreover, islets from individuals with T2DM released substantial amounts of inflammatory cytokines and chemokines such as IL-6, IL-8, CXCL1, granulocyte colony-stimulating factor (G-CSF) and macrophage inflammatory protein 1 α (MIP1 α)²⁴. Although these data showed a correlation between the abundance of macrophages and increased inflammatory cytokines, the cellular origins of these cytokines and their roles in β -cell function remained undetermined.

Further work has been carried out to characterize obesity-associated islet inflammation using various rodent models. For example, leptin receptor-deficient *db/db* mice, which are obese and used as a model of T2DM, have substantially increased accumulation of islet macrophages compared with wild-type mice. Further characterization showed that CD68⁺F4/80⁺ macrophages found in the pancreas of *db/db* mice exhibited a pro-inflammatory M1-like phenotype³². In the same study, a new and less typical CD68⁺F4/80⁺ macrophage population was also found in the islets of humans with T2DM. Another study using a palmitate acid-induced obesity model reported that saturated fatty acids (SFAs) induced β -cells to produce chemokines that attracted CD11b⁺Ly6C⁺ M1-like pro-inflammatory monocytes and macrophages to the islets¹⁰. An in-depth assessment of obesity-associated metaflammation carried out using diet-induced and genetically induced mouse models of obesity found that obesity-associated islet inflammation is dominated by macrophages, with negligible involvement of adaptive immune cells¹² (FIG. 1).

Thus, macrophages in islets and in the exocrine stroma of the pancreas are distinct in origin and phenotypic properties. Whether this variation is due to location or different lineages is uncertain; however, the

Yolk sac-derived primitive haematopoiesis

The generation of blood-lineage cells, including primitive erythroid cells, platelets and macrophages, in the extra-embryonic yolk sac during early embryonic development.

Osteopetrosis

A rare inherited syndrome characterized by increased bone density due to a defect of osteoclasts, a specialized population of macrophages that can resorb bone.

Insulinitis

Islet-specific inflammation characterized by the infiltration of various types of immune cell into pancreatic islets, more commonly used to describe the islet inflammation preceding or accompanying type 1 diabetes mellitus.

Islet amyloid polypeptide

(IAPP). An islet hormone that is co-secreted with insulin from β -cells and forms islet amyloids.

Metaflammation

Low-grade inflammation induced by overnutrition, which occurs in metabolic tissue (primarily adipose tissue, liver, muscle and pancreatic islets), causes dysregulation of immune cells and inflammatory responses.

Box 1 | Physiological and pathophysiological roles of islet macrophages

Noninflammatory state

- Intra-islet macrophages and peri-islet macrophages^{12,17}
- Supports islet (β -cell) development and regeneration^{15–17}
- Promotes glucose-stimulated insulin secretion¹²
- Low concentration of IL-1 β ^{10,17,104,109}

Obesity and type 2 diabetes mellitus

- Increased number of intra-islet macrophages^{10,12,24,27,32}
- Promotes compensatory β -cell proliferation¹²
- Suppresses glucose-stimulated insulin secretion with decreased expression of β -cell-specific genes^{10,12,61,62}
- Elevated production of IL-1 β ^{10,51,61}

cellular reconstitution after irradiation experiments suggests that tissue location has a key role in programming macrophages to gain specific phenotypes and functions¹².

Causes of islet macrophage accumulation

Tissue-resident macrophages are populated from several waves of precursors during the embryonic stage and are self-maintained during adulthood^{13,33}. However, during inflammation and tissue injury, bone marrow-derived monocytes can infiltrate tissues and differentiate into macrophages³⁴.

Obesity induces local proliferation of islet macrophages.

Interestingly, intra-islet and peri-islet macrophage populations are maintained in lean mice at a very low turnover rate¹². This finding is consistent with a previous report showing that, at steady state, islet macrophages are only minimally derived from circulating blood cells and instead replicate locally at a low rate¹⁷. However, under obese conditions, local proliferation of islet-resident macrophages in mice was substantially increased¹². These findings suggest a new mechanism of intra-islet macrophage accumulation in obese mice. Local proliferation has also been demonstrated for adipose tissue macrophages (ATMs) under obese conditions in mice^{35–38}. In addition, reports suggest that IL-6 (REF.³⁵), CCL2 (REF.³⁷), CSF1 (REF.³⁹) or osteopontin³⁸ could stimulate ATM replication in animals.

Macrophages can adapt to local environmental cues^{40,41} and intra-islet-resident macrophage proliferation could possibly be an adaptive response to pathophysiological stimuli. However, the factors that mediate this adaptation remain to be defined. An interesting question is whether elevated plasma glucose and/or fatty acid levels in obesity can trigger the release of stimulating factors within the islets that activate the local proliferation of islet macrophages.

Circulating monocytes and islet macrophages. During chronic inflammation, circulating monocytes infiltrate and accumulate in inflamed tissue sites. Whether an infiltration of circulating monocytes can also explain obesity-associated islet inflammation is an important question. In a SFA treatment mouse model, ethyl palmitate infusion significantly increased the number of

CD11b⁺Ly6C⁺ monocytes found in pancreatic islets¹⁰. However, the exact distribution of these monocytes (that is, intra-islet or peri-islet) was not determined. Importantly, adoptive transfer experiments showed that transferred fluorescently labelled Ly6C⁺ monocytes infiltrated to the boundary between the exocrine and endocrine pancreas but did not penetrate into the islets in HFD-fed obese mice¹². Furthermore, these transferred cells retained their monocyte phenotype and did not differentiate into macrophages in the pancreas. Interestingly, time-course analysis showed that these peri-islet monocytes eventually migrate to pancreas-draining lymph nodes¹² (FIG. 1). However, the lack of penetration of transferred monocytes into the HFD islets might be due to the lack of an available tissue niche. Indeed, a previous study reported that monocytes can replace islet macrophages in mice after lethal irradiation¹⁷.

The initiating factors for islet inflammation. An important and unanswered question is what triggers islet inflammation in obesity. As obesity is associated with systemic low-grade inflammation, systemic metabolic or inflammatory factors could potentially impinge on the islet microenvironment. For example, in vitro high-glucose stimulation can induce IL-1 β secretion from islets through activation of the NLRP3 inflammasome^{42,43}. Circulating SFAs could also induce islet inflammation, particularly in the presence of hyperglycaemia^{10,44,45}. Although circulating cytokine levels are often increased in obesity and diabetes mellitus, these cytokines serve primarily as biomarkers of systemic inflammation, as the concentration of circulating cytokines is much lower than the biologically active levels that occur within the local tissue microenvironment. The blood concentration of cytokines such as tumour necrosis factor (TNF) or IL-1 β are 10-fold to 100-fold lower than the levels required to induce pro-inflammatory biological effects and are therefore unlikely to trigger obesity-induced islet inflammation^{46–50}.

Alternatively, islet-derived local signals could also have an important role in initiating the inflammatory cascade⁵¹. For example, islet-resident macrophages could act as first-line responders to sense systemic metabolic changes. As a consequence, these macrophages could alter their function and/or expand locally. However, β -cells have been suggested to be early responders (mentioned earlier in the Review) as these cells can sense excessive fatty acids and produce chemokines to recruit Ly6C⁺ monocytes and macrophages to pancreatic islets¹⁰. Moreover, ATP released from stressed β -cells has been reported to lead to macrophage activation⁵².

In patients with T2DM, aggregated IAPP can induce pro-inflammatory responses in islet macrophages. For example, synthetic human IAPP (hIAPP) treatment or the use of an hIAPP transgenic mouse model showed that hIAPP can increase the synthesis of IL-1 β in islet-resident macrophages⁵³. Whether islet macrophages, β -cells or both are the first responders to metabolic insults remains unclear; however, local interactions between these two cell types seem to accelerate the inflammatory process.

Type 2 innate lymphoid cells (ILC2s). A subgroup of innate lymphoid cells characterized by the lack of rearranged receptors and production of type 2 cytokines such as IL-5 and IL-13.

Transcriptional profile of islet macrophages. Obesity affects islet macrophage transcriptomes, which results in altered functions. Earlier studies reported that macrophages within the islets of obese mice exhibited a pro-inflammatory, M1-like phenotype^{10,32}. However, a 2015 study found that, in lean mice, islet-resident macrophages constitutively expressed M1-associated cytokines, including IL-1 β and TNF¹⁷. Furthermore, in a 2019 study¹², RNA sequencing analysis of isolated macrophages from lean and obese mice showed no clear shift between M1-like and M2-like profiles in either intra-islet or peri-islet macrophage subsets. Interestingly, islet macrophages in leptin receptor-deficient *db/db* mice have been proposed to show a shift from an early stage (8 weeks of age) pro-inflammatory phenotype towards late-stage (28 weeks of age) profibrotic characteristics³². Thus, during the development of obesity and T2DM, the nature of islet inflammation is not simply polarization from an M2-like to an M1-like state (BOX 2) but instead is a mixed continuum of heterogeneous cell phenotypes. Consistent with this notion, in adipose tissue of obese mice, ATMs exhibit diverse phenotypes across a broad spectrum of M1-like and M2-like polarization states^{54–56}.

Other immune and nonimmune cells. A few studies reported the presence of T cells and B cells^{29,57} in pancreatic islets of humans with T2DM. By contrast, another study did not detect the presence of T cells or B cells in the islets of HFD-fed mice, which is evidence against the involvement of the adaptive immune system in obesity-associated islet pathology¹². However, T cells can be detected in the exocrine pancreas at very low

abundance, and a HFD did not alter their number¹². Another study reported that type 2 innate lymphoid cells (ILC2s) were present in the islets of lean mice and that an HFD reduced the number of these cells in the islets. These cells stimulated insulin secretion through retinoic acid produced by islet myeloid cells⁵⁸. Furthermore, an IL-33–ILC2 axis was activated after acute β -cell stress but was defective during chronic obesity⁵⁸. Thus, other types of immune cell might be involved in obesity-associated islet inflammation in a model- or stage-dependent manner. In addition, islet endothelial cells and neurons also have important roles in modulating the islet microenvironment, which can influence β -cell function^{52,59}. For example, central nervous system modulation of islet function has been reported, and islet endothelial cell-derived vascular endothelial growth factor (VEGF) might affect β -cell replication⁶⁰ (also see the section on Recovery of β -cell mass after injury or acute β -cell depletion).

Effects on β -cell function

The following section discusses potential effects of islet macrophages on β -cell function. The deficit of β -cell function in T2DM is characterized by decreased β -cell mass and impaired glucose-stimulated insulin secretion (GSIS)⁶¹. Incubation of primary human islets or β -cell lines with pro-inflammatory cytokines, such as IL-1 β or TNF, increases β -cell apoptosis and decreases GSIS⁶². By contrast, clodronate liposome-mediated depletion of macrophages in the islets of HFD-fed mice improves GSIS¹². Consistent with this finding, systemic depletion of tissue macrophages by in vivo administration of clodronate liposomes improves glucose tolerance in obese mice¹⁰. The full mechanisms by which islet macrophages impair GSIS are not clearly understood; however, it probably involves both macrophage-derived soluble factors and direct cell–cell contact between islet macrophages and β -cells (FIG. 2).

Soluble factors. The levels of several cytokines, such as TNF and IL-1 β , are increased in obese and T2DM islets in humans and suppress β -cell GSIS^{62,63}. The best-studied cytokine produced by islet macrophages is IL-1 β . Of note, β -cells express the IL-1 receptor (IL-1R) and obesity increases IL-1 β expression in islet macrophages in both mice and humans^{10,64}. In vitro incubation of mouse and human monocyte/macrophage cell lines in media containing high concentrations of glucose or free fatty acids (FFAs) induces increased IL-1 β production. This suggests that metabolic stress in obesity and/or T2DM can stimulate islet macrophages to produce more IL-1 β ^{10,65,66}. Indeed, while both β -cells and macrophages can produce IL-1 β , macrophages are seemingly the major source of islet IL-1 β production in obesity^{10,64}.

Incubation of primary human or mouse islets, or β -cell lines, with IL-1 β decreases GSIS and increases β -cell apoptosis⁶². Moreover, the secretion of inflammatory cytokines from islet macrophages that are cocultured with Min6 cells amplifies the lipotoxic effects of chronic palmitate treatment, decreasing GSIS and expression of the genes involved in β -cell differentiation and function¹⁰. Furthermore, the increased lipotoxic

Box 2 | Protective and harmful inflammation

Inflammation is an adaptive response exploited by the host to deal with harmful conditions²². Acute inflammation is commonly associated with infection, whereas chronic inflammation is widely associated with more complex disorders, such as diabetes mellitus and cardiovascular diseases^{18,19,21}. Evolutionarily, inflammation is a beneficial protective mechanism to eliminate infectious pathogens, elicit tissue repair and restore tissue homeostasis²². By contrast, chronic, low-grade inflammation is generally thought to result in pathological consequences in the targeted tissue or cell, such as functional impairment, cell death and tissue damage⁹.

Macrophages are key players in orchestrating the initiation, specification and resolution of tissue inflammation^{9,22,23}. Macrophages are heterogeneous in terms of their origin, tissue phenotype and function¹²⁴. By adapting to tissue environmental cues, macrophages can acquire different functionalities and are programmed into pro-inflammatory (sometimes referred to as M1-like), anti-inflammatory (sometimes referred to as M2-like) or reparative states.

Dissecting the phenotypic and functional heterogeneity of islet macrophages and the interactions between macrophages and β -cells will improve our understanding of obesity and type 2 diabetes mellitus. This knowledge could lead to the development of new immunomodulatory regimens to prevent or reverse these disorders.

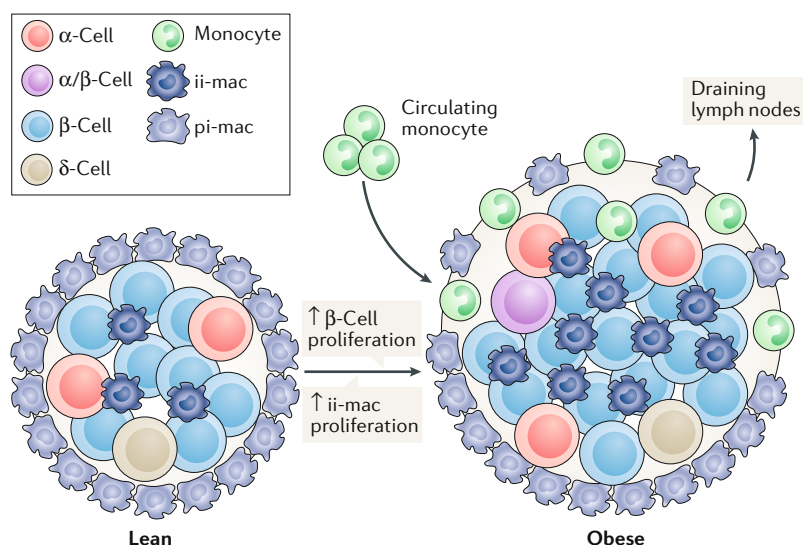


Fig. 1 | Macrophages dominate obesity-associated islet inflammation. A comparison of mouse islets between lean and obese conditions. In lean mice, two major populations of macrophages can be detected based on their anatomical distributions: peri-islet macrophages (pi-macs; F4/80^{hi}CD11c⁻) and intra-islet macrophages (ii-macs; F4/80^{lo}CD11c^{hi})¹². Both populations are islet-resident cells. By contrast, in obesity, the size of islets is increased owing to increased β -cell replication and cell size. Different mechanisms have been proposed to explain obesity-associated macrophage accumulation in the islet. In one model, stressed β -cells recruit circulating monocytes, which differentiate into pro-inflammatory macrophages after infiltrating into the islets. This model has been challenged by other studies showing that even though monocytes can be detected in the pancreas they do not infiltrate into the islets¹⁰. Instead, the accumulation of ii-macs is caused by local proliferation of resident macrophages¹².

effects of FFAs on β -cells by coculture with macrophages is ameliorated by the addition of neutralizing antibodies against the pro-inflammatory cytokines TNF and IL-1 β to the culture media¹⁰.

The intracellular events through which inflammation impairs β -cell function involve the JNK and nuclear factor- κ B (NF- κ B) signalling pathways. For example, TNF-induced NF- κ B activation in INS-1 rat insulinoma cells decreases GSIS⁶⁷. In addition, activation of NF- κ B in β -cells can reduce expression of an ER Ca²⁺ pump (sarcoplasmic reticulum Ca²⁺ ATPase type 2b), which leads to ER stress and decreased GSIS⁶⁸.

Unlike TNF and IFN γ , IL-1 β also stimulates JNK in β -cell lines^{69–72}. IL-1 β -induced JNK activation decreases GSIS by suppressing the insulin receptor substrate (IRS)–phosphoinositide 3-kinase (PI3K)–AKT signalling pathway. This results in reduced FOXO1 phosphorylation, with increased nuclear localization of active FOXO1 and decreased DNA binding to PDX1 (REFS^{73–75}). These findings are important as research suggests that normal FOXO1 function is necessary for maintenance of the full β -cell differentiation state⁷⁶. In addition, a study showed that combination IL-1 β –TNF–IFN γ treatment of human islets and INS-1 cells can result in β -cell apoptosis by inducing mitochondrial stress and activation of proapoptotic BCL-2 family proteins⁷⁷.

IL-1 β treatment of primary rat β -cells does not fully recapitulate the gene expression changes induced by glucolipotoxicity, which suggests that some divergence of mechanisms might also exist^{78,79}. Another study reported

data that questioned the importance of IL-1 β in human islets, showing that in vitro treatment with high glucose concentrations (11 and 28 mmol/l), did not induce IL-1 β production or NF- κ B activation⁸⁰. Together, these results indicate the existence of other factors and mechanisms involved in high glucose or FFA-induced β -cell dysfunction.

Cell–cell contacts. Another mechanism by which macrophages can decrease β -cell insulin secretion is through direct cell–cell contact. For example, co-incubation of the Min6 β -cell line with intra-islet macrophages isolated from HFD-fed mice decreases GSIS¹². Interestingly, this effect was seen only when the macrophages were directly added to the Min6 cells. Preventing direct cell–cell contact by culturing the two cell types in Transwell plate chambers, which still allow interactions through soluble factors, blocks the impairment in GSIS¹². These results suggest that the inhibitory effect of intra-islet macrophages on β -cell GSIS includes a cell–cell contact process. The concept of β -cell–macrophage interactions through direct cell–cell contacts is not new. Islet macrophages can engulf insulin secretory vesicles in a mouse model of T1DM⁸¹. Similar to these findings, mouse intra-islet macrophages contain intact insulin secretory vesicles, and the number of engulfed vesicles was greatly increased in obesity¹².

The mechanism by which islet macrophages incorporate insulin secretory vesicles from β -cells and how obesity accelerates this process remains unclear. However, macrophages can generate open-ended channels called tunnelling nanotubes, which transport cytoplasmic materials between connected cells⁸². Therefore, tunnelling nanotubes could theoretically mediate macrophage uptake of β -cell secretory granules, and obesity and islet inflammation might increase this process (FIG. 2). The potential transport of macrophage-derived factors to β -cells through these nanotubes might also affect β -cell insulin secretion. It is also possible that extracellular vesicles or gap junctions are involved in the crosstalk between macrophages and β -cells.

Effects on β -cell proliferation

In adult humans, the turnover rate of β -cells is extremely low. However, β -cells are not permanently quiescent. Under certain conditions, such as pregnancy and obesity, these cells are able to re-enter the cell cycle^{12,83}. In addition, adaptive expansion of β -cell mass has been observed in obese, insulin-resistant mice and humans^{84–88}. Multiple factors, including increased plasma glucose concentrations^{89–91}, insulin⁹² and expression of hepatocyte growth factor^{93–95}, can stimulate β -cell replication. Evidence now exists suggesting that macrophages can have an important role in β -cell replication.

Recovery of β -cell mass after injury or acute β -cell depletion.

An increasing body of evidence has supported a role for macrophages in β -cell expansion. For example, in a pancreatic injury mouse model induced by partial duct ligation, islet macrophages were observed to increase β -cell proliferation through transforming growth factor (TGF) and downstream SMAD7 signalling⁹⁶.

Transwell plate chambers

Devices designed to study cell migration and cell–cell interaction, which are permeable to soluble factors but prevent the migration or contact of cells between the upper and lower chambers.

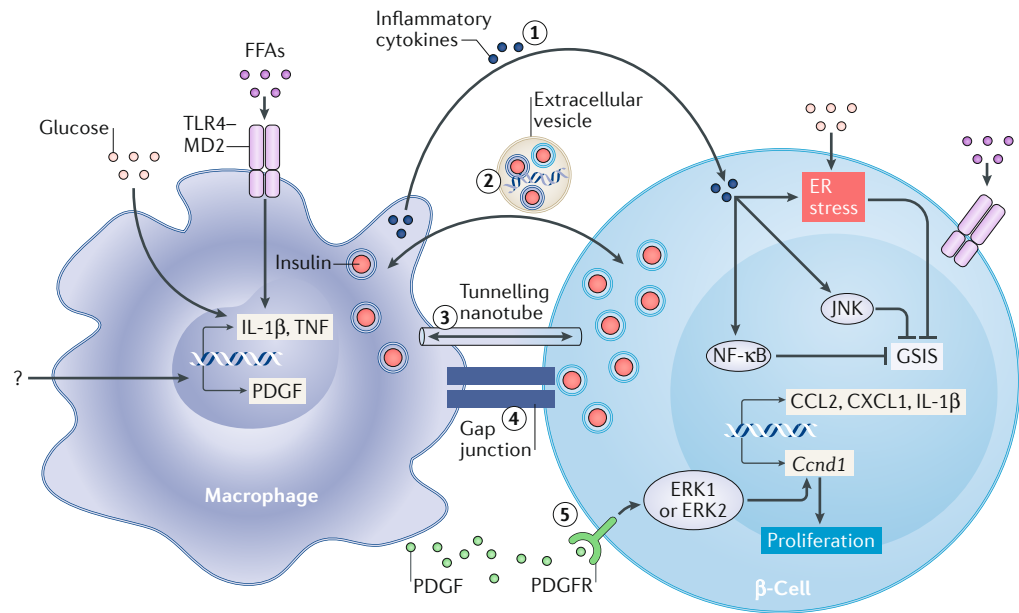


Fig. 2 | Interactions of islet macrophages and β -cells in obesity. An increasing body of evidence supports the idea that islet macrophages influence β -cells in multiple ways. In obesity, elevated plasma levels of glucose and free fatty acids (FFAs) can induce a pro-inflammatory phenotype of islet macrophages. As a result, macrophages produce increased amounts of pro-inflammatory cytokines such as IL-1 β and tumour necrosis factor (TNF). These cytokines activate nuclear factor- κ B (NF- κ B) and JNK pathways in β -cells and also exacerbate endoplasmic reticulum (ER) stress (1)^{67,68}. Synergistically, these responses dampen β -cell glucose-stimulated insulin secretion (GSIS). In addition to inflammatory cytokines, other mechanisms involving macrophage-mediated β -cell dysfunction exist. The mechanisms include extracellular vesicles containing insulin released by β -cells and phagocytosed by islet macrophages (2)¹²; and the formation of tunnelling nanotubes (3) or gap junctions (4) between macrophages and β -cells, allowing for bidirectional exchange of cellular contents. Obesity increases platelet-derived growth factor (PDGF) expression in islet macrophages via unclear mechanisms¹². Through PDGF receptors (PDGFRs) expressed in β -cells, PDGF promotes β -cell proliferation by activating downstream extracellular signal-regulated kinase (ERK) signalling and inducing cell cycle gene (for example, *Ccnd1*) expression (5)⁹⁸. MD2, myeloid differentiation factor 2; TLR4, Toll-like receptor 4.

By contrast, depletion of islet macrophages in vivo in a mouse model, or ex vivo in isolated pancreatic islets, by clodronate liposome treatment results in a decreased number of proliferating bromodeoxyuridine-positive β -cells⁹⁶.

Using a mouse model with 50% β -cell depletion, followed by β -cell-specific overexpression of connective tissue growth factor, researchers found that β -cells release connective tissue growth factor as a chemoattractant to recruit macrophages, which then facilitate the recovery of β -cell mass⁹⁷. In another study, transiently increased expression of VEGFA in β -cells led to β -cell loss, and withdrawal of VEGFA stimulated a robust but transient increase in the proliferation of pre-existing β -cells⁵⁹. Moreover, bone marrow-derived macrophages were recruited to the site of β -cell injury and are important for β -cell proliferation⁵⁹. Taken together, these studies indicate that macrophages have a critical role in maintaining steady state β -cell mass and facilitate increased β -cell proliferation and mass in pathophysiological insulin-resistant states.

β -Cell proliferation in obesity. Obesity-induced insulin resistance induces an expansion of pancreatic β -cells, which compensate by secreting increased quantities of insulin. Islet macrophages from obese mice show an increased capacity to stimulate β -cell proliferation and

both intra-islet and peri-islet macrophages show similar effects. This effect was mediated by platelet-derived growth factor (PDGF)–PDGF receptor (PDGFR) signalling¹². Thus, the PDGF–PDGFR pathway has an important role in mouse and human β -cell proliferation⁹⁸. Of note, one study suggests that the reduction of PDGFR signalling in β -cells accounts for the decline in β -cell replication in aged mice and older humans⁹⁸. Macrophages are a major source of PDGF^{99–102} and the expression of *Pdgfa* was increased in both CD11c⁺ intra-islet macrophages and CD11c⁺ peri-islet macrophages in obese mice¹². Furthermore, inhibition of PDGFR signalling in vitro with a small-molecule inhibitor, CP-673451, blocked the effect of islet macrophages to stimulate β -cell replication¹². Therefore, in addition to the expression of PDGFR on β -cells, the production of PDGF by islet macrophages forms a signalling system that induces β -cell proliferation (FIG. 2).

Proinflammatory cytokines. Proinflammatory cytokines, such as TNF and IL-1 β , are key components of the islet inflammatory microenvironment³¹, and the role of IL-1 β has been extensively studied¹⁰³. Knockout of β -cell IL-1R in vivo causes β -cell dedifferentiation¹⁰⁴. In addition, low concentrations (0.01–0.02 ng/ml) of IL-1 β can induce β -cell proliferation in vitro by activating the FAS–FLIP antiapoptotic pathway¹⁰⁵. Moreover, lean

IL-1 receptor antagonist (IL-1Ra). A member of the IL-1 family of cytokines that binds to the IL-1 receptor but does not induce intracellular signalling.

mice that lack IL-1 β production show downregulation of FAS–FLIP activation as well as decreased β -cell proliferation¹⁰⁵.

In contrast, at high concentrations (1 ng/ml), IL-1 β can suppress the expression of genes associated with a fully differentiated β -cell phenotype in human and mouse islets¹⁰⁶. This effect can facilitate β -cell apoptosis and can also induce β -cell dedifferentiation into islet endocrine cells, which express and secrete both insulin and glucagon¹⁰⁷. These latter dual-positive endocrine cells¹⁰⁷ generally demonstrate impaired GSIS in vivo, which provides another potential mechanism whereby IL-1 β adversely affects β -cell GSIS¹⁰⁶. Given all of these findings, the IL-1 β 'tone' within the islet provides an important control point for regulation of β -cell mass.

In humans, IL-1 receptor antagonist (IL-1Ra) expression is increased in the blood during obesity and T2DM but is decreased in islets from patients with T2DM^{108,109}. In mice, β -cell-specific IL-1Ra ablation resulted in a reduction in β -cell proliferation and impaired insulin secretion¹⁰⁹. In addition, decreased plasma levels of IL-1Ra promotes IL-1 β signalling and studies have shown that treatment of Goto–Kakizaki rats with IL-1Ra led to a reduction in islet inflammation and improved β -cell GSIS. Taken together, these results provide compelling evidence for the role of the inflammatory cytokine IL-1 β in islet inflammation and β -cell dysfunction.

Beneficial effects on β -cells

While depletion of islet macrophages improves GSIS in HFD-fed obese mice, macrophage depletion decreases β -cell GSIS in normal islets from lean chow-fed mice¹². This finding suggests that, in the normal lean state, islet macrophages might have a beneficial role in β -cell insulin secretion. The mechanism (or mechanisms) by which islet macrophages from lean and obese mice have seemingly opposite roles in β -cell function remains unclear. In obesity, islet macrophages might be reprogrammed to impair β -cell GSIS, which could be due to effects of FFAs, glucose or cytokines, such as IL-1 β .

One possible explanation for the metabolism-dependent effects of islet macrophages is the level of IL-1 β that they produce. For example, islet macrophages in nonobese mice exhibit a pro-inflammatory activation state and produce IL-1 β ¹⁷. However, the acute postprandial rise in IL-1 β production by myeloid cells has been demonstrated to contribute to meal-induced insulin secretion in a fasting–refeeding mouse model and is necessary for normal glycaemic control¹¹⁰. In line with this, IL-1R1-deficient mice exhibited an impaired adaptive increase in plasma insulin levels after HFD feeding¹¹¹. However, chronic accumulation or elevated production of IL-1 β (mainly by islet macrophages) is detrimental to β -cell GSIS¹⁰³.

In addition to IL-1 β , other factors and mechanisms could also have a role in shifting the effect of islet macrophages on β -cells. For instance, pathways related to synapse formation were more activated in islet macrophages in obese mice than in lean mice¹², suggesting that obesity alters cell–cell interaction between macrophages and β -cells.

The above discussion raises several questions. First, what induces islet macrophages to change their effects on β -cell GSIS in the transition from the lean to the obese state? Second, at which stage of obesity does this functional switch of islet macrophages happen? Third, what modifications can reverse the macrophage-mediated 'detrimental' effects on β -cells? To answer these questions, it will be necessary to perform longitudinal studies that can elucidate the functional properties of islet macrophages and assess the effects of these cells on β -cell function in a stage-dependent manner.

Lipids as mediators of crosstalk

Several studies have indicated that SFAs and potentially lipoproteins are circulating factors that might contribute to islet inflammation, β -cell dysfunction and β -cell hyperplasia^{10,44,45}. For example, experimental elevation of palmitate levels in mice induces islet inflammation¹⁰. Moreover, the same study showed that in vivo treatment with SFAs increased the accumulation of islet macrophages and other markers of islet inflammation and also decreased GSIS.

SFAs activate intracellular pro-inflammatory pathways by binding to the innate immune receptor Toll-like receptor 4 (TLR4). Studies show that TLR4 is required for the SFA-induced effect on islet inflammation and further show that TLR4 expressed on islet macrophages was essential for this process¹⁰. The SFAs act on macrophage TLR4 to stimulate the NF- κ B pathway, resulting in cytokine secretion, particularly of IL-1 β and TNF, which can negatively influence β -cell GSIS¹⁰. TLR4 is also expressed on β -cells, and SFAs can bind to this receptor and induce β -cells to secrete chemokines and other factors, which stimulate islet macrophage accumulation¹⁰.

In addition to these effects of SFAs on β -cell secretory functions, elevated SFA levels can also affect β -cell proliferation¹⁰. This effect is particularly true when elevated SFA levels are combined with hyperglycaemia, as this combination appears to cause additive effects on β -cell proliferation. Of note, apoptosis negatively regulates overall β -cell mass and, within the islet, SFAs can be converted to ceramides, which induce apoptosis^{112,113}. Furthermore, exposure to palmitate is reported to trigger human β -cell apoptosis by inducing death protein 5-mediated ER stress¹¹⁴. Thus, by inducing apoptosis and stimulating proliferation, SFAs might have important effects on increasing overall β -cell mass in the context of obesity and T2DM.

Another interesting connection between circulating lipoproteins and β -cell function has been reported. LDL receptor-related protein 1 (LRP1) can interact with extracellular lipoproteins, and one research group generated β -cell-specific LRP1-deficient mice and showed that these animals were partially protected from the adverse effects of a HFD on β -cell insulin secretion, as well as HFD-induced β -cell hyperplasia⁴⁵. The same study also found that this could be related to the effect of LRP1 deletion to upregulate β -cell peroxisome proliferator-activated receptor- γ 2 (PPAR γ 2) in HFD-fed mice, as transgenic overexpression of PPAR γ 2 in β -cells partially recapitulated the LRP1 phenotype.

Senescence

Cellular senescence is characterized by stable cell cycle arrest and a pro-inflammatory senescence-associated secretory phenotype¹¹⁵. The current theory is that the senescent signal can spread from one senescent cell to other surrounding cells; however, the mechanism remains to be resolved. Some indications suggest that individuals with T1DM and the nonobese diabetic (NOD) mouse model harbour a set of senescent β -cells that express increased levels of the prosurvival mediator BCL-2 (REF.¹¹⁶). Interestingly, treatment with a BCL-2 inhibitor can efficiently deplete senescent β -cells and prevent the occurrence of T1DM in the NOD mouse model¹¹⁶.

Obesity could potentially induce a β -cell senescence response, which might drive the pathogenesis of T2DM. For example, an earlier study found that the number of acidic β -galactosidase-positive senescent β -cells was increased in HFD-fed mice¹¹⁷. More recently, a 2017 study found that insulin resistance can induce a senescent state in both mouse and human β -cells, which leads to decreased insulin secretion¹¹⁸. Consistent with this idea, the number of senescent β -cells is increased in islets from patients with T2DM¹¹⁸. However, it remains unknown whether islet macrophages also develop senescent phenotypes in the context of obesity or whether senescent β -cells can regulate islet macrophage activation.

Clinical studies

A number of clinical trials targeting inflammatory pathways have been tested in patients with T2DM, including the salicylic acid derivative salsalate and anti-inflammatory TNF inhibitors^{119,120}. In some clinical trials, the effects of these interventions on β -cells have been assessed. For example, in one double-blind, parallel group trial involving 70 patients with T2DM, the administration of the recombinant IL-1Ra anakinra confers a moderate but statistically significant decrease in fasting blood glucose and HbA_{1c} (−0.3 to −0.4%) levels¹²¹. Furthermore, anakinra treatment increases insulin secretion from β -cells without affecting insulin sensitivity. The larger scale CANTOS trial included individuals with prior myocardial infarction and high-sensitivity C-reactive protein and used an anti-IL-1 β

antibody (canakinumab)¹²². They demonstrated that IL-1 β neutralization lowers plasma HbA_{1c} levels during the first 6–9 months of treatment but does not reduce the incidence of new-onset diabetes mellitus¹²². As canakinumab treatment substantially reduces the recurrence of cardiovascular events, these results suggest that anti-inflammatory therapy can provide beneficial effects for individuals with obesity and/or T2DM. A meta-analysis performed in 2019 of 2,921 individuals from eight phase I–IV studies found a statistically significant overall HbA_{1c}-lowering effect of IL-1 antagonism, achieved through either anti-IL-1 antibodies or IL-1R antagonists¹²³. In this meta-analysis, a statistically significant correlation between baseline C-reactive protein and C-peptide, and HbA_{1c} outcomes was also revealed. However, the authors also cautioned that the identification of further biomarkers is needed to define the potential of anti-IL-1 therapies in T2DM.

Conclusions

Islet inflammation has emerged as a key feature of obesity and T2DM; in these conditions islet macrophages are the defining immune cell type. Although much has been learned about macrophage– β -cell interactions, many important questions remain unresolved. For example, the triggering events with respect to islet macrophage proliferation and expansion are unclear. Moreover, it is not clear whether the initiating signals are derived from the β -cell or whether they are extrinsic to the islet. Of note, islet macrophage proliferation is not significantly increased in mice until after 12–16 weeks of an HFD¹². If β -cell insulin secretory function is affected prior to this time, then what is the cause? Have macrophages already started to reprogramme into a pathogenic phenotype before proliferation ensues or does a macrophage-independent mechanism cause the initial defect in GSIS? In addition, it is not currently clear why circulating monocytes migrate to the peri-islet area but do not enter the islets. Finally, more information is needed on the role of islet inflammation and macrophages in the insulin secretory defects that characterize human T2DM.

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- da Rocha Fernandes, J. et al. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. *Diabetes Res. Clin. Pract.* **117**, 48–54 (2016).
- Knowler, W. C. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
- Magkos, F. et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab.* **23**, 591–601 (2016).
- Saisho, Y. Importance of beta cell function for the treatment of type 2 diabetes. *J. Clin. Med.* **3**, 923–943 (2014).
- Kitamura, T. The role of FOXO1 in beta-cell failure and type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **9**, 615–623 (2013).
- Biden, T. J., Boslem, E., Chu, K. Y. & Sue, N. Lipotoxic endoplasmic reticulum stress, beta cell failure, and type 2 diabetes mellitus. *Trends Endocrinol. Metab.* **25**, 389–398 (2014).
- Donath, M. Y. & Shoelson, S. E. Type 2 diabetes as an inflammatory disease. *Nat. Rev. Immunol.* **11**, 98–107 (2011).
- Lackey, D. E. & Olefsky, J. M. Regulation of metabolism by the innate immune system. *Nat. Rev. Endocrinol.* **12**, 15–28 (2016).
- Lee, Y. S., Wollam, J. & Olefsky, J. M. An integrated view of immunometabolism. *Cell* **172**, 22–40 (2018).
- Eguchi, K. et al. Saturated fatty acid and TLR signaling link beta cell dysfunction and islet inflammation. *Cell. Metab.* **15**, 518–533 (2012).
- This study shows that SFAs induce β -cells to produce chemokines that recruit pro-inflammatory monocytes and macrophages, which impair β -cell function.**
- Boni-Schnetzler, M. & Meier, D. T. Islet inflammation in type 2 diabetes. *Semin. Immunopathol.* **41**, 501–513 (2019).
- Ying, W. et al. Expansion of islet-resident macrophages leads to inflammation affecting beta cell proliferation and function in obesity. *Cell Metab.* **29**, 457–474 e455 (2019).
- This study reports that resident macrophages drive obesity-associated islet inflammation through local proliferation and that the accumulated islet macrophages affect both β -cell proliferation and function.**
- Ginhoux, F. & Williams, M. Tissue-resident macrophage ontogeny and homeostasis. *Immunity* **44**, 439–449 (2016).
- Schulz, C. et al. A lineage of myeloid cells independent of Myb and hematopoietic stem cells. *Science* **336**, 86–90 (2012).
- Geutskens, S. B., Otonkoski, T., Pulkkinen, M. A., Drexhage, H. A. & Leenen, P. J. Macrophages in the murine pancreas and their involvement in fetal endocrine development in vitro. *J. Leukoc. Biol.* **78**, 845–852 (2005).
- Banaei-Bouchareb, L. et al. Insulin cell mass is altered in Csf1op/Csf1op macrophage-deficient mice. *J. Leukoc. Biol.* **76**, 359–367 (2004).
- Calderon, B. et al. The pancreas anatomy conditions the origin and properties of resident macrophages. *J. Exp. Med.* **212**, 1497–1512 (2015).
- This study provides a comprehensive view of the origin, phenotype, turnover and gene expression of macrophages in exocrine pancreas and the islets.**
- Mathis, D. Immunological goings-on in visceral adipose tissue. *Cell Metab.* **17**, 851–859 (2013).
- McLaughlin, T., Ackerman, S. E., Shen, L. & Engleman, E. Role of innate and adaptive immunity in obesity-

- associated metabolic disease. *J. Clin. Invest.* **127**, 5–13 (2017).
20. Sell, H., Habich, C. & Eckel, J. Adaptive immunity in obesity and insulin resistance. *Nat. Rev. Endocrinol.* **8**, 709–716 (2012).
 21. Shalpour, S. & Karin, M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J. Clin. Invest.* **125**, 3347–3355 (2015).
 22. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
 23. Murray, P. J. & Wynn, T. A. Protective and pathogenic functions of macrophage subsets. *Nat. Rev. Immunol.* **11**, 723–737 (2011).
 24. Ehses, J. A. et al. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes* **56**, 2356–2370 (2007).
- This study provides clear evidence showing an increase in the number of macrophages in the islets of humans with T2DM and animal models of obesity and T2DM.**
25. Kamata, K. et al. Islet amyloid with macrophage migration correlates with augmented beta-cell deficits in type 2 diabetic patients. *Amyloid* **21**, 191–201 (2014).
 26. Zhao, H. L. et al. Prevalence and clinicopathological characteristics of islet amyloid in Chinese patients with type 2 diabetes. *Diabetes* **52**, 2759–2766 (2003).
 27. Richardson, S. J., Willcox, A., Bone, A. J., Foulis, A. K. & Morgan, N. G. Islet-associated macrophages in type 2 diabetes. *Diabetologia* **52**, 1686–1688 (2009).
 28. Marselli, L. et al. Beta-cell inflammation in human type 2 diabetes and the role of autophagy. *Diabetes* **52**, 130–136 (2013).
 29. Butcher, M. J. et al. Association of proinflammatory cytokines and islet resident leucocytes with islet dysfunction in type 2 diabetes. *Diabetologia* **57**, 491–501 (2014).
 30. Donath, M. Y., Storling, J., Berchtold, L. A., Billestrup, N. & Mandrup-Poulsen, T. Cytokines and beta-cell biology: from concept to clinical translation. *Endocr. Rev.* **29**, 334–350 (2008).
 31. Eguchi, K. & Nagai, R. Islet inflammation in type 2 diabetes and physiology. *J. Clin. Invest.* **127**, 14–23 (2017).
 32. Cucak, H., Grunnet, L. G. & Rosendahl, A. Accumulation of M1-like macrophages in type 2 diabetic islets is followed by a systemic shift in macrophage polarization. *J. Leukoc. Biol.* **95**, 149–160 (2014).
 33. Perdiguer, E. G. & Geissmann, F. The development and maintenance of resident macrophages. *Nat. Immunol.* **17**, 2–8 (2016).
 34. Ginhoux, F. & Jung, S. Monocytes and macrophages: developmental pathways and tissue homeostasis. *Nat. Rev. Immunol.* **14**, 392–404 (2014).
 35. Braune, J. et al. IL-6 regulates M2 polarization and local proliferation of adipose tissue macrophages in obesity. *J. Immunol.* **198**, 2927–2934 (2017).
 36. Haase, J. et al. Local proliferation of macrophages in adipose tissue during obesity-induced inflammation. *Diabetologia* **57**, 562–571 (2014).
 37. Amano, S. U. et al. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. *Cell Metab.* **19**, 162–171 (2014).
 38. Tardelli, M. et al. Osteopontin is a key player for local adipose tissue macrophage proliferation in obesity. *Mol. Metab.* **5**, 1131–1137 (2016).
 39. Hamilton, J. A. Colony-stimulating factors in inflammation and autoimmunity. *Nat. Rev. Immunol.* **8**, 533–544 (2008).
 40. Gosselin, D. et al. Environment drives selection and function of enhancers controlling tissue-specific macrophage identities. *Cell* **159**, 1327–1340 (2014).
 41. Lavin, Y. et al. Tissue-resident macrophage enhancer landscapes are shaped by the local microenvironment. *Cell* **159**, 1312–1326 (2014).
 42. Zhou, R., Tardivel, A., Thorens, B., Choi, I. & Tschopp, J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat. Immunol.* **11**, 136–140 (2010).
 43. Maedler, K. et al. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. *J. Clin. Invest.* **110**, 851–860 (2002).
 44. Boni-Schnetzler, M. et al. Free fatty acids induce a proinflammatory response in islets via the abundantly expressed interleukin-1 receptor I. *Endocrinology* **150**, 5218–5229 (2009).
 45. Ye, R. et al. Intracellular lipid metabolism impairs beta cell compensation during diet-induced obesity. *J. Clin. Invest.* **128**, 1178–1189 (2018).
 46. Amar, S., Zhou, Q., Shaik-Dasthagirsah, Y. & Leeman, S. Diet-induced obesity in mice causes changes in immune responses and bone loss manifested by bacterial challenge. *Proc. Natl Acad. Sci. USA* **104**, 20466–20471 (2007).
47. Zhang, Q. et al. NF-kappaB dynamics discriminate between TNF doses in single cells. *Cell Syst.* **5**, 638–645.e5 (2017).
 48. Turner, D. A. et al. Physiological levels of TNFalpha stimulation induce stochastic dynamics of NF-kappaB responses in single living cells. *J. Cell Sci.* **123**, 2834–2843 (2010).
 49. Stephens, J. M., Lee, J. & Pilch, P. F. Tumor necrosis factor-alpha-induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression without a loss of insulin receptor-mediated signal transduction. *J. Biol. Chem.* **272**, 971–976 (1997).
 50. McGillicuddy, F. C. et al. Lack of interleukin-1 receptor I (IL-1R) protects mice from high-fat diet-induced adipose tissue inflammation coincident with improved glucose homeostasis. *Diabetes* **60**, 1688–1698 (2011).
 51. Aamodt, K. I. & Powers, A. C. Signals in the pancreatic islet microenvironment influence beta-cell proliferation. *Diabetes* **56**, 124–136 (2007).
 52. Weitz, J. R. et al. Mouse pancreatic islet macrophages use locally released ATP to monitor beta cell activity. *Diabetologia* **61**, 182–192 (2018).
 53. Westwell-Roper, C. Y., Ehses, J. A. & Verchere, C. B. Resident macrophages mediate islet amyloid polypeptide-induced islet IL-1beta production and beta-cell dysfunction. *Diabetes* **63**, 1698–1711 (2014).
 54. Kratz, M. et al. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. *Cell Metab.* **20**, 614–625 (2014).
 55. Lumeng, C. N., DelProposto, J. B., Westcott, D. J. & Saltiel, A. R. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. *Diabetes* **57**, 3239–3246 (2008).
 56. Li, P. et al. Functional heterogeneity of CD11c-positive adipose tissue macrophages in diet-induced obese mice. *J. Biol. Chem.* **285**, 15333–15345 (2010).
 57. Rodriguez-Calvo, T., Ekwil, O., Amirian, N., Zapardiel-Gonzalo, J. & von Herrath, M. G. Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. *Diabetes* **63**, 3880–3890 (2014).
 58. Dalmas, E. et al. Interleukin-33-activated islet-resident innate lymphoid cells promote insulin secretion through myeloid cell retinoic acid production. *Immunity* **47**, 928–942.e7 (2017).
 59. Brissova, M. et al. Islet microenvironment, modulated by vascular endothelial growth factor-A signaling, promotes beta cell regeneration. *Cell Metab.* **19**, 498–511 (2014).
- This study demonstrates the importance of endothelial cell-derived VEGF in regulating beta-cell proliferation and insulin secretion.**
60. Porte, D. Jr., Baskin, D. G. & Schwartz, M. W. Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from C. elegans to humans. *Diabetes* **54**, 1264–1276 (2005).
 61. Halban, P. A. et al. Beta-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. *Diabetes Care* **37**, 1751–1758 (2014).
- This paper briefly summarizes recent knowledge on the mechanisms underlying beta-cell failure in T2DM.**
62. Donath, M. Y., Boni-Schnetzler, M., Ellingsgaard, H., Halban, P. A. & Ehses, J. A. Cytokine production by islets in health and diabetes: cellular origin, regulation and function. *Trends Endocrinol. Metab.* **21**, 261–267 (2010).
 63. Burns, S. M. et al. High-throughput luminescent reporter of insulin secretion for discovering regulators of pancreatic beta-cell function. *Cell Metab.* **21**, 126–137 (2015).
 64. Westwell-Roper, C., Denroche, H. C., Ehses, J. A. & Verchere, C. B. Differential activation of innate immune pathways by distinct islet amyloid polypeptide (IAPP) aggregates. *J. Biol. Chem.* **291**, 8908–8917 (2016).
 65. Dasu, M. R., Devaraj, S. & Jialal, I. High glucose induces IL-1beta expression in human monocytes: mechanistic insights. *Am. J. Physiol. Endocrinol. Metab.* **293**, E337–E346 (2007).
 66. Riera-Borrull, M. et al. Palmitate conditions macrophages for enhanced responses toward inflammatory stimuli via JNK activation. *J. Immunol.* **199**, 3858–3869 (2017).
 67. Kim, H. E. et al. Tumour necrosis factor-alpha-induced glucose-stimulated insulin secretion inhibition in INS-1 cells is ascribed to a reduction of the glucose-stimulated Ca²⁺ influx. *J. Endocrinol.* **198**, 549–560 (2008).
68. Cardozo, A. K. et al. Cytokines downregulate the sarcoplasmic reticulum pump Ca²⁺ ATPase 2b and deplete endoplasmic reticulum Ca²⁺, leading to induction of endoplasmic reticulum stress in pancreatic beta-cells. *Diabetes* **54**, 452–461 (2005).
 69. Major, C. D. & Wolf, B. A. Interleukin-1beta stimulation of c-Jun NH₂-terminal kinase activity in insulin-secreting cells: evidence for cytoplasmic restriction. *Diabetes* **50**, 2721–2728 (2001).
 70. Ammendrup, A. et al. The c-Jun amino-terminal kinase pathway is preferentially activated by interleukin-1 and controls apoptosis in differentiating pancreatic beta-cells. *Diabetes* **49**, 1468–1476 (2000).
 71. Bonny, C., Oberon, A., Negri, S., Sausser, C. & Schorderet, D. F. Cell-permeable peptide inhibitors of JNK: novel blockers of beta-cell death. *Diabetes* **50**, 77–82 (2001).
 72. Welsh, N. Interleukin-1 beta-induced ceramide and diacylglycerol generation may lead to activation of the c-Jun NH₂-terminal kinase and the transcription factor ATF2 in the insulin-producing cell line RINm5F. *J. Biol. Chem.* **271**, 8307–8312 (1996).
 73. Bouzakri, K. et al. Rab GTPase-activating protein AS160 is a major downstream effector of protein kinase B/Akt signaling in pancreatic beta-cells. *Diabetes* **57**, 1195–1204 (2008).
 74. Kawamori, D. et al. The forkhead transcription factor Foxo1 bridges the JNK pathway and the transcription factor PDX-1 through its intracellular translocation. *J. Biol. Chem.* **281**, 1091–1098 (2006).
 75. Kaneto, H. et al. Involvement of c-Jun N-terminal kinase in oxidative stress-mediated suppression of insulin gene expression. *J. Biol. Chem.* **277**, 30010–30018 (2002).
 76. Kim-Muller, J. Y. et al. Metabolic inflexibility impairs insulin secretion and results in MODY-like diabetes in triple FoxO-deficient mice. *Cell Metab.* **20**, 593–602 (2014).
 77. Grunnet, L. G. et al. Proinflammatory cytokines activate the intrinsic apoptotic pathway in beta-cells. *Diabetes* **58**, 1807–1815 (2009).
 78. Cardozo, A. K., Kruoffer, M., Leeman, R., Orntoft, T. & Eizirik, D. L. Identification of novel cytokine-induced genes in pancreatic beta-cells by high-density oligonucleotide arrays. *Diabetes* **50**, 909–920 (2001).
 79. Weir, G. C., Laybutt, D. R., Kaneto, H., Bonner-Weir, S. & Sharma, A. Beta-cell adaptation and decompensation during the progression of diabetes. *Diabetes* **50**, S154–S159 (2001).
 80. Welsh, N. et al. Is there a role for locally produced interleukin-1 in the deleterious effects of high glucose or the type 2 diabetes milieu to human pancreatic islets? *Diabetes* **54**, 3238–3244 (2005).
 81. Vomund, A. N. et al. Beta cells transfer vesicles containing insulin to phagocytes for presentation to T cells. *Proc. Natl Acad. Sci. USA* **112**, E5496–E5502 (2015).
- This study shows evidence that intra-islet macrophages take up intact insulin-containing vesicles from beta-cells.**
82. Yamashita, Y. M., Inaba, M. & Buszczak, M. Specialized intercellular communications via cytonemes and nanotubes. *Annu. Rev. Cell. Dev. Biol.* **34**, 59–84 (2018).
 83. Baeyens, L., Hindi, S., Sorenson, R. L. & German, M. S. Beta-cell adaptation in pregnancy. *Diabetes* **56**, 63–70 (2007).
 84. Hull, R. L. et al. Dietary-fat-induced obesity in mice results in beta cell hyperplasia but not increased insulin release: evidence for specificity of impaired beta cell adaptation. *Diabetologia* **48**, 1350–1358 (2005).
 85. Peyot, M. L. et al. Beta-cell failure in diet-induced obese mice stratified according to body weight gain: secretory dysfunction and altered islet lipid metabolism without steatosis or reduced beta-cell mass. *Diabetes* **59**, 2178–2187 (2010).
 86. Ebato, C. et al. Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. *Cell Metab.* **8**, 325–332 (2008).
 87. Stamateris, R. E., Sharma, R. B., Hollern, D. A. & Alonso, L. C. Adaptive beta-cell proliferation increases early in high-fat feeding in mice, concurrent with metabolic changes, with induction of islet cyclin D2 expression. *Am. J. Physiol. Endocrinol. Metab.* **305**, E149–E159 (2013).
 88. Mosser, R. E. et al. High-fat diet-induced beta-cell proliferation occurs prior to insulin resistance in

- C57BL/6J male mice. *Am. J. Physiol. Endocrinol. Metab.* **308**, E573–E582 (2015).
89. Alonso, L. C. et al. Glucose infusion in mice: a new model to induce beta-cell replication. *Diabetes* **56**, 1792–1801 (2007).
 90. Levitt, H. E. et al. Glucose stimulates human beta cell replication in vivo in islets transplanted into NOD-severe combined immunodeficiency (SCID) mice. *Diabetologia* **54**, 572–582 (2011).
 91. Porat, S. et al. Control of pancreatic beta cell regeneration by glucose metabolism. *Cell Metab.* **13**, 440–449 (2011).
 92. Assmann, A., Ueki, K., Winnay, J. N., Kadowaki, T. & Kulkarni, R. N. Glucose effects on beta-cell growth and survival require activation of insulin receptors and insulin receptor substrate 2. *Mol. Cell Biol.* **29**, 3219–3228 (2009).
 93. Garcia-Ocana, A. et al. Hepatocyte growth factor overexpression in the islet of transgenic mice increases beta cell proliferation, enhances islet mass, and induces mild hypoglycemia. *J. Biol. Chem.* **275**, 1226–1232 (2000).
 94. Araujo, T. G. et al. Hepatocyte growth factor plays a key role in insulin resistance-associated compensatory mechanisms. *Endocrinol.* **153**, 5760–5769 (2012).
 95. Demirci, C. et al. Loss of HGF/c-Met signaling in pancreatic beta-cells leads to incomplete maternal beta-cell adaptation and gestational diabetes mellitus. *Diabetes* **61**, 1143–1152 (2012).
 96. Xiao, X. et al. M2 macrophages promote beta-cell proliferation by up-regulation of SMAD7. *Proc. Natl Acad. Sci. USA* **111**, E1211–E1220 (2014).
This study reveals that M2-like macrophages and the SMAD7 pathway can increase β -cell mass.
 97. Riley, K. G. et al. Macrophages are essential for CTGF-mediated adult beta-cell proliferation after injury. *Mol. Metab.* **4**, 584–591 (2015).
 98. Chen, H. et al. PDGF signalling controls age-dependent proliferation in pancreatic beta-cells. *Nature* **478**, 349–355 (2011).
 99. Jaguin, M., Fardel, O. & Lecureur, V. AhR-dependent secretion of PDGF-BB by human classically activated macrophages exposed to DEP extracts stimulates lung fibroblast proliferation. *Toxicol. Appl. Pharmacol.* **285**, 170–178 (2015).
 100. Onogi, Y. et al. PDGFR β regulates adipose tissue expansion and glucose metabolism via vascular remodeling in diet-induced obesity. *Diabetes* **66**, 1008–1021 (2017).
 101. Shimokado, K. et al. A significant part of macrophage-derived growth factor consists of at least two forms of PDGF. *Cell* **43**, 277–286 (1985).
 102. Zhou, X. et al. Circuit design features of a stable two-cell system. *Cell* **172**, 744–757.e17 (2018).
 103. Donath, M. Y., Dalmas, E., Sauter, N. S. & Boni-Schnetzler, M. Inflammation in obesity and diabetes: islet dysfunction and therapeutic opportunity. *Cell Metab.* **17**, 860–872 (2013).
 104. Burke, S. J. et al. Pancreatic deletion of the interleukin-1 receptor disrupts whole body glucose homeostasis and promotes islet beta-cell de-differentiation. *Mol. Metab.* **14**, 95–107 (2018).
This study reports that knockout of the β -cell IL-1 β receptor in mice can result in dedifferentiation of β -cells.
 105. Maedler, K. et al. Low concentration of interleukin-1 beta induces FLICE-inhibitory protein-mediated beta-cell proliferation in human pancreatic islets. *Diabetes* **55**, 2713–2722 (2006).
This study shows an improvement in β -cell proliferation by a low concentration of IL-1 β .
 106. Nordmann, T. M. et al. The role of inflammation in beta-cell dedifferentiation. *Sci. Rep.* **7**, 6285 (2017).
 107. Talchai, C., Xuan, S., Lin, H. V., Sussel, L. & Acili, D. Pancreatic beta cell dedifferentiation as a mechanism of diabetic beta cell failure. *Cell* **150**, 1223–1234 (2012).
 108. Boni-Schnetzler, M. et al. Increased interleukin (IL)-1 beta messenger ribonucleic acid expression in beta-cells of individuals with type 2 diabetes and regulation of IL-1 beta in human islets by glucose and autostimulation. *J. Clin. Endocrinol. Metab.* **93**, 4065–4074 (2008).
 109. Boni-Schnetzler, M. et al. Beta cell-specific deletion of the IL-1 receptor antagonist impairs beta cell proliferation and insulin secretion. *Cell Rep.* **22**, 1774–1786 (2018).
This study provides evidence supporting an important role of β -cell-derived IL-1Ra on β -cell function and maintenance.
 110. Dror, E. et al. Postprandial macrophage-derived IL-1 beta stimulates insulin, and both synergistically promote glucose disposal and inflammation. *Nat. Immunol.* **18**, 283–292 (2017).
This study indicates the physiological role of macrophage-derived IL-1 β in mediating postprandial β -cell insulin secretion.
 111. Hajmrlc, C. et al. Interleukin-1 signaling contributes to acute islet compensation. *JCI Insight* **1**, e86055 (2016).
 112. Kelpe, C. L. et al. Palmitate inhibition of insulin gene expression is mediated at the transcriptional level via ceramide synthesis. *J. Biol. Chem.* **278**, 30015–30021 (2003).
 113. Lang, F., Ullrich, S. & Gulbins, E. Ceramide formation as a target in beta-cell survival and function. *Expert Opin. Ther. Targets* **15**, 1061–1071 (2011).
 114. Cunha, D. A. et al. Death protein 5 and p53-upregulated modulator of apoptosis mediate the endoplasmic reticulum stress-mitochondrial dialog triggering lipotoxic rodent and human beta-cell apoptosis. *Diabetes* **61**, 2763–2775 (2012).
 115. Tchonia, T., Zhu, Y., van Deursen, J., Campisi, J. & Kirkland, J. L. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J. Clin. Invest.* **123**, 966–972 (2013).
 116. Thompson, P. J. et al. Targeted elimination of senescent beta cells prevents type 1 diabetes. *Cell Metab.* **29**, 1045–1060.e10 (2019).
This study demonstrates the critical role of senescent β -cells in triggering the occurrence of T1DM.
 117. Sone, H. & Kagawa, Y. Pancreatic beta cell senescence contributes to the pathogenesis of type 2 diabetes in high-fat diet-induced diabetic mice. *Diabetologia* **48**, 58–67 (2005).
 118. Aguayo-Mazzucato, C. et al. Beta cell aging markers have heterogeneous distribution and are induced by insulin resistance. *Cell Metab.* **25**, 898–910.e5 (2017).
This study reveals the development of senescent β -cells that affect insulin secretion in obesity and/or T2DM.
 119. Donath, M. Y. Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat. Rev. Drug Discov.* **13**, 465–476 (2014).
 120. Goldfine, A. B. et al. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. *Ann. Intern. Med.* **159**, 1–12 (2013).
 121. Larsen, C. M. et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N. Engl. J. Med.* **356**, 1517–1526 (2007).
 122. Everett, B. M. et al. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J. Am. Coll. Cardiol.* **71**, 2392–2401 (2018).
This study provides a critical assessment of the effect of canakinumab on major cardiovascular events among individuals with and without diabetes mellitus.
 123. Kataria, V., Ellervik, C. & Mandrup-Poulsen, T. Treatment of type 2 diabetes by targeting interleukin-1: a meta-analysis of 2921 patients. *Semin. Immunopathol.* **41**, 413–425 (2019).
 124. Gordon, S. & Pluddemann, A. Tissue macrophages: heterogeneity and functions. *BMC Biol.* **15**, 53 (2017).

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Competing interests

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